

FUSION CONSTRUCTS AND METHODS OF USING THEREOF

BACKGROUND OF THE DISCLOSURE

[0001] Recently, monoclonal antibody-based cancer immunotherapy based on the interruption of suppressive signals that are delivered to the adaptive immune system has shown promise in the clinic. With the FDA approval of CTLA-4 antibody inhibitor (e.g., ipilimumab) and PD-1 inhibitors (e.g., pembrolizumab, nivolumab), more treatment options are now available to treat solid tumors including lung cancer, renal cell cancer, and ovarian cancer. However, in the majority of indications where PD-1/PD-L1 and TGF- β are co-expressed (e.g., ovarian, gastric and colorectal) little to no response to immune checkpoint inhibitors has been observed. Accordingly, there is a continuing need in the art to obtain safer and more effective treatments for cancer.

INCORPORATION BY REFERENCE

[0002] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY OF THE DISCLOSURE

[0003] Provided herein is a fusion protein comprising: (a) a first component that is an antibody, or a fragment or variant thereof; and (b) a second component that is: (i) a cytokine trap, or fragment or variant thereof; or (ii) an adenosine deaminase (ADA), or fragment or variant.

[0004] In certain embodiments, first component is an immunoglobulin G (IgG) antibody, for example an IgG1, IgG2, IgG3, or IgG4 antibody. In certain embodiments, the antibody is an IgG1 or IgG4 antibody.

[0005] In certain embodiments, the antibody fragment of the first component is a Fab, (Fab)₂, (Fab')₂, Fv, (Fv)₂, or scFv.

[0006] In certain embodiments, the antibody, or fragment or variant thereof, of the first component comprises a variable region of a heavy chain (V_H) and a variable region of a light chain (V_L).

[0007] In certain embodiments, the antibody, or fragment or variant thereof, of the first component comprises a fragment crystallizable region (F_C), for example an F_C1, F_C2, F_C3, or F_C4 region, or a fragment or variant thereof. In certain embodiments, the antibody, or fragment or variant thereof, comprises an F_C1 region. In certain embodiments, the F_C comprises at least one mutation.

[0008] In certain embodiments, the antibody, or fragment or variant thereof, of the first component comprises a scFv and an F_C.

[0009] In certain embodiments, the antibody, or fragment or variant thereof, of the first component binds to a tumor antigen expressed on the surface of a tumor cell. Examples of such a tumor antigen include CD19, BCMA, CD23, BAFF-R, GPRC5D, CD44, CAIX, CD5, CD30, CD70, CD44v6, CD44v7, CD44v8, CD174, CD28, CD128, CD138, CS1, CLL-1, L1-CAM, FAP, ROR1, CEA, EGP-2, EGP-40, HER2, HER3, Folate-binding Protein, GD2, GD3, IL-13R- α 2, IL-11R α , EphA2, CSPG4, KDR, EDB-F, mesothelin, CD22, EGFR, Folate receptor α , MUC-1, MUC-4,

MUC-16, MAGE-A1, h5T4, PSMA, PSCA, GPC3, c-met, TAG-72, EGFR, CD20, EGFRvIII, CD123, and VEGF-R2. In certain embodiments, the tumor antigen is a mucin, for example a MUC1, MUC2, MUC3A, MUC3B, MUC4, MUC5AC, MUC5B, MUC6, MUC7, MUC8, MUC12, MUC13, MUC15, MUC16, MUC17, MUC19, or MUC20 antigen.

[0010] In certain embodiments, the antibody, or fragment or variant thereof, of the first component binds to MUC16. For example, the antibody, or fragment or variant thereof, may comprise a V_L region comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 417-428 and/or a V_H region comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 390-403. In certain embodiments, the antibody, or fragment or variant thereof, comprises a V_H region comprising a sequence that is at least 80% identical to SEQ ID NO: 399 and/or a V_L region comprising a sequence that is at least 80% identical to SEQ ID NO: 426. In certain embodiments, the antibody, or fragment or variant thereof, comprises a heavy chain sequence that is at least 80% identical to SEQ ID NO: 441 and/or a light chain sequence that is at least 80% identical to SEQ ID NO: 443.

[0011] In certain embodiments, the antibody, or fragment or variant thereof, of the first component binds to MUC1. For example, the antibody, or fragment or variant thereof, may comprise a V_L region comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 449-453, and/or a V_H region comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 444-448. In certain embodiments, the antibody, or fragment or variant thereof, comprises a V_H region comprising a sequence that is at least 80% identical to SEQ ID NO: 444. In certain embodiments, the antibody, or fragment or variant thereof, comprises a V_H region comprising a sequence that is at least 80% identical to SEQ ID NO: 444 and a V_L region comprising a sequence that is at least 0% identical to any one of SEQ ID NOs: 449-453. In certain embodiments, the antibody, or fragment or variant thereof, comprises a heavy chain sequence that is at least 80% identical to SEQ ID NO: 466 and/or a light chain sequence that is at least 80% identical to SEQ ID NO: 467.

[0012] In certain embodiments, the antibody, or fragment or variant thereof, of the first component binds to programmed cell death protein-1 (PD-1). Such an antibody will be referred to herein as an "anti-PD-1 antibody."

[0013] In certain embodiments, the antibody of the first component is an IgG4 antibody comprising a sequence having at least 80% sequence identity to SEQ ID NO: 146 or 292 and having a mutation at position 108 thereof. For example, the antibody may be an IgG4 antibody comprising a sequence having at least 80% sequence identity to SEQ ID NO: 146 or 292 and having a S108P mutation (i.e., amino acid proline in place of serine at position 108).

[0014] In certain embodiments, the antibody, or fragment or variant thereof, of the first component comprises a V_H or a V_L that is connected to the second component by a linker.

[0015] In certain embodiments, the antibody, or fragment or variant thereof, of the first component comprises a V_H and a V_L and the V_H and V_L are connected to each other by a second linker, for example one comprising a sequence of any one of SEQ ID NOs: 17-34.

[0016] In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, comprises a V_H Comprising a